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● *Clinical Investigation*

REDUCTION OF RADIOACTIVE SEED EMBOLIZATION TO THE LUNG FOLLOWING PROSTATE BRACHYTHERAPY

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Purpose: Ultrasound-guided interstitial implantation of radioactive seeds is a common treatment for early stage prostate cancer. One of the risks associated with this therapy is seed embolization to the lung. This paper reports on the incidence and possible adverse effects of seed migration.

Methods and Materials: Two hundred ninety consecutive patients were treated with permanent radioactive seed brachytherapy for prostate cancer between January 1 and December 31, 1995. One hundred fifty-four patients were treated with iodine-125 (I-125), and 136 patients were treated with palladium-103 (Pd-103). All but one patient had a routine post implant chest radiograph (CXR), leaving 289 evaluable patients.

Results: Twenty radioactive seed pulmonary emboli were identified in 17 patients; 3 patients had two emboli each. The radioactive seed pulmonary embolism rate for the entire group of patients was 5.9%. Acute pulmonary symptoms were not reported by any patient in this series. One hundred forty-six study patients were implanted with free seeds alone (136 Pd-103 and 11 I-125), and 143 were implanted with linked seed embedded in a vicryl suture for the peripheral portions of their implants. The radioactive seed embolization rate by patient was 11% (16/146) versus 0.7% (1/143) for free seed implants and implants utilizing linked seeds, respectively. The difference was statistically significant, $p = 0.0002$. No patient had detectable morbidity as a consequence of seed emboli.

Conclusion: The use of linked seeds embedded in vicryl sutures for the peripheral portion of permanent radioactive seed prostate implants significantly reduced the incidence of pulmonary seed embolization in patients treated with the Seattle technique. © 1998 Elsevier Science Inc.

Brachytherapy, Pulmonary embolism, Prostate, Palladium-103, Iodine-125.

INTRODUCTION

Prostate cancer will affect 1 in 9 American men during the course of their lifetime (1). While there are many options for treatment, the Prostate Cancer Clinical Guidelines Panel of the American Urologic Association endorses radical surgery, external beam radiation therapy, and interstitial brachytherapy as standard treatment for localized forms of the disease (2). Each of these treatments has it associated benefits and risks (3, 4). One of the risks associated with permanent seed brachytherapy is seed embolization to the lung (5–8).

Radioactive seed pulmonary embolization from prostate brachytherapy was previously described by Steinfeld *et al.* (9). The exact mechanism of embolization is not clear; however, to ensure adequate radiation dose to the prostate, seeds are often implanted near or outside of the prostatic capsule. The prostate is surrounded by a dense venous plexus, and seeds placed into these veins may hematogenously migrate to distal sites, including the lung. This mechanism may be similar to the hematagenous dissemination of cancer cells (10). Possible adverse effects of this seed migration include a reduction in radiation dose to the prostate (11) and possible, but unknown, adverse effects on lung tissue.

The purpose of this paper is to report the incidence and the possible adverse effects of radioactive seed embolization to the lungs, and to assess the effect of using linked seeds embedded in a braided, hardened suture material (vicryl) on the rate of radioactive seed pulmonary embolization in a series of patients implanted with I-125 or Pd-103 seeds for prostate cancer.

METHODS AND MATERIALS

The records from all patients treated for prostate cancer with brachytherapy at Northwest Hospital in Seattle, WA,

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between January 1 and December 31, 1995 were reviewed. The time frame was arbitrarily chosen. Two hundred ninety patients were treated during this time period; all but one had routine post-treatment chest radiographs the day following implantation. The specific purpose of the radiographs was to screen for radioactive seed pulmonary embolization. Excluding the one patient who did not have a post treatment chest radiograph, 289 patients were eligible for review. The radiologist's report routinely specified the presence or absence of radioactive seed emboli, when not specified in the report, the radiographs were reviewed with a diagnostic radiologist.

The ultrasound-guided transperineal template implantation techniques used in this series of patients have been previously described (12–14). A philosophy of modified uniform seed distribution, which weights between 10–20% of the activity to the periphery of the gland was adopted. The practice was to use a relatively large number of seeds, each with relatively low activity, thus placing less reliance on any individual seed toward the required dose and distribution. All implants were pre-planned. A margin of 2–5 mm outside of the prostate was usually included in the target volume. This margin often included portions of the periprostatic venous plexus.

Forty-five eligible patients were treated with combined external beam irradiation followed by a brachytherapy boost. Two hundred forty-four patients were treated with brachytherapy alone. One hundred thirty-six patients were implanted with Pd-103 (115 Gy) and 153 patients were implanted with I-125 (160 Gy). The radioactive source strength varied from 0.28 to 0.37 mCi per seed for I-125, and 1.0–1.4 mCi per seed for Pd-103. Pd-103 and I-125 seeds possess identical dimensions but differ slightly in the shape of the ends because of different welding techniques. Pd-103 and I-125 were implanted with identical techniques.

I-125 is commercially available as either free seeds or as Rapid Strand™, linked, embedded seeds spaced 1 cm apart in a braided, stiffened vicryl suture. Palladium-103 is available only as free seeds. Fisher's exact test was used to determine the level of significance between groups.

One hundred forty-three patients were implanted with linked seeds. These linked seeds were restricted to needles placed at the periphery of the prostate implant. All seeds placed centrally, close to the urethra, were free seeds. On average, 8–10 free seeds were used in I-125 implants that were performed with linked seeds; thus, no patient was treated without al least some free seeds. Ten eligible patients were implanted with free I-125 seeds only. All 136 patients implanted with Pd-103 were implanted only with free seeds.

Both free seeds and linked seeds were pre-loaded into 18-gauge implant needles prior to the procedure according to the dosimetry plan. Free seeds were alternated with pre-cut 5.5 mm absorbable plain gut spacer material to maintain spacing of 1 cm between seed centers. Linked seeds are spaced at 1 cm intervals along the stiffened vicryl material and were cut to the desired number of seeds for each needle.

Table 1. Radioactive seed pulmonary embolization rates

	No. Embolized/ Patients	Embolizaiton rate %	*p* value
Isotope			
Pd-103 (free seeds)	15/136	11	n/a
I-125 (free seeds)	1/10	10	
I-125 (linked seeds)	1/143	0.7	
TOTAL	17/289	5.9	
Seed loading			
Free seeds	16/146	11	0.0002
Linked seeds	1/143	0.7	

RESULTS

Seventeen patients had a total of twenty radioactive seed emboli detected in the lungs. The overall pulmonary embolization rate was 5.9 % (17/289). Three patients had two embolization events each, one to each lung. The seeds were found in the periphery of the lungs; 12 seeds embolized to the right lung and 8 seeds embolized to the left lung.

The rate of pulmonary seed embolization by isotope was 11% (15/136) for free Pd-103 seeds and 0.7% (1/143) for linked I-125 seeds (Table 1). One (10%) of the ten eligible patients implanted only with free I-125 seeds had a pulmonary seed embolus (Table 1). Table 1 compares the seed pulmonary embolization rate for patients implanted only with free seeds (both Pd-103 and I-125) to those implanted with linked seeds embedded in vicryl. The embolization rate for all free seed only implants was 11% (16/146) compared to 0.7% (1/143) for patients implanted with linked seeds. The difference is statistically significant ($p = 0.0002$). No difference was observed in embolization rates between patients treated with combined external beam radiation therapy and brachytherapy compared to patients treated with brachytherapy alone.

Acute pulmonary symptoms such as pain, cough, or dispense were not reported by any patient during or after the implant procedure. With a follow-up of 2 years, no patient has reported subsequent symptoms or sequelae related to seed pulmonary emboli. Surgical removal of embolized seeds has not been performed in any patient. Although none have been observed, it is too early to evaluate possible late effects from radioactive seed pulmonary embolism.

DISCUSSION

For over a decade it has been recognized that prostate tissue is an unpredictable matrix for holding radioactive seeds (15). Free seeds may rotate in tissue and potentially

embolize through the vascular system. Therefore, it was thought that linked seeds would be less subject to these uncertainties of source position following implantation. In 1986, Kumar described the use of linked I-125 seeds for prostate brachytherapy using flexible vicryl carrier (15). van't Riet described the use of linked I-125 seeds in a stiffened vicryl carrier for prostate brachytherapy, which resulted in a more accurate seed arrangement, but the issue of pulmonary seed embolization was not addressed (16). The use of seeds in a stiffened vicryl carrier has been further developed and refined by one of the authors (PG). This series represents our experience using linked I-125 seeds with particular reference to pulmonary seed emboli.

The periprostatic venous plexus flanks the prostate gland laterally and anteriorly, and theoretically serves as ready access for radioactive seed embolus. This venous complex drains into the iliac vessels, then into the inferior vena cava and eventually into the right side of the heart and to the lungs. Migration of radioactive seeds to other organs, such as the brain, would require active communication between the right and left chambers of the heart, such as a right-to-left shunt.

Migration of seeds beyond the prostate has been observed fluoroscopically at the time of implantation. It is likely that this migration occurs as a result of seed placement within the large lumens of the periprostatic venous plexus. In this study, the CXR was taken the day following implantation and therefore represents immediate or early pulmonary seed migration. In a study reported by Nag *et al.* (5), pulmonary seed migration was noted in 19 of 112 patients evaluated. Ten of the 19 were noted to have immediate pulmonary seed migration. In this report, 9 of 19 patients with seed pulmonary embolization had them detected on CXR taken 28–127 days post implant, all of these patients had an earlier post-implant CXR that failed to document a seed emboli. Delayed migration of seeds may have less dosimetric impact on the prostate and deliver less radiation to the adjacent lung tissue.

Two potential problems arise from radioactive seed embolization: (1) alteration of prostate dosimetry, and (2) adverse effects for lung tissue irradiation.

Alteration of prostate dosimetry

The technique developed in Seattle for prostate cancer brachytherapy usually results in 80–110 implanted seeds per patient. The advantage of using many, but lower activity seeds, is that the dose to any one point is less dependent on any single seed. The loss of a single seed therefore has less impact on the dosimetry. Extra seeds are always available in the operating room to be placed in any deficient areas as noted by ultrasonography or fluoroscopy. With this dosimetric approach, it is doubtful that the loss of 1 or 2 seeds would have a significant effect on the dose homogeneity or total dose to the prostate. Post-implant dosimetry was routinely performed from pelvic computed tomography scans and pelvic radiographs performed the day following implantation. No patient required supplemental seed insertion because of seed loss through pulmonary embolization in this series. Implant techniques which use a fewer number but higher activity seeds may be more vulnerable to seed migration as the dose to any point is largely dependent on the dose from the nearest seed (11).

Table 2. Dosimetric calculations for an anisotropic I-125 seed

Distance from source (cm)	Dose to H_2O (Gy)	Dose to lung (Gy)	Volume encompassed (cc)
0.5	31.68	30.73	0.5
1.0	7.78	7.86	4.2
2.0	1.63	1.94	33.5
3.0	0.56	0.82	113.1
4.0	0.23	0.43	268.1
5.0	0.1	0.25	523.6

Lung density corrections were made for these points by applying dose correction factors as described by Prasad (22), assuming an electron density of 0.25 (e- per gram) for typical lung tissue (23, 24). Volume encompassed for each dose is based on $4/3\ \pi\ r^3$.

Potential adverse effects on lung tissue

The implications of lung irradiation from embolized seeds are not known. Potential complications include pneumonitis and carcinogenesis. With average energies of 28 keV and 21 keV for I-125 and Pd-103 respectively, the volume of lung receiving a significant dose is approximately 1 cc. Table 2 lists the calculated doses to points along a transverse radius of a I-125 seed with a strength of 0.34 mCi, using the recent AAPM Task Group 43 dosimety parameters and formalism (17). Even with multiple emboli, such volumes would be unlikely to have any measurable effect on pulmonary function.

Radioactive seed pulmonary embolization appears to be an asymptomatic event. Resultant morbidity was not observed in our series, and has not been reported in the literature. As many as five seeds have been reported to embolize in a single patient without detectable toxicity (9). The maximum number of seed emboli in a single patient in our series was two. The most serious potential complication of seed migration would be embolization of a seed to the brain. This event, which would require a right to left vascular shunt has not been observed.

The development of a cancer in the lung as a result of the seed embolization is a potential more serious consequence. Patients who have received external beam radiation for Hodgkin's disease, breast cancer, or individuals receiving low chronic doses of radiation in their working environment are known to have an increased risk of lung cancer (18, 19). Since many factors are involved in the development of a cancer from radiation (dose, dose rate, radiation quality, irradiated volume, etc.), the risk of developing a cancer from a radioactive seed emboli is difficult to predict (20, 21). There has been no reported case of a lung cancer

secondary to seed emboli, but the follow-up time is short. Although it is possible to remove an embolized seed by thoracotomy or thoroscopy, the associated surgical risk and morbidity would likely outweigh any possible benefit.

While no detrimental effects have been demonstrated to date, efforts should be made to reduce the incidence of radioactive seed pulmonary embolism as long as these efforts do not compromise the effectiveness of the prostate implant. The use of linked seed can reduce the incidence of seed pulmonary emboli. We believe that using seeds on an absorbable strand is most beneficial at the periphery, where seed embolization is more likely to occur. In the central portions of the gland we choose to use free seeds. This central portion of the gland is uniform in texture and good seed distribution is seen. Centrally placed seeds occasionally lodge in the urethral mucosa and can be removed cystoscopically to prevent focal overdosing. A free seed lodged in the urethral mucosa can be easily removed, while linked seeds in the urethra generally require removal of the entire strand. Removal of an entire strand would be too traumatic and may compromise the prostate radiation dose. These centrally placed free seeds could theoretically gain entrance to the periprostatic venous plexus at the cephalad or caudad margin of the prostate, thus accounting for the 0.7% incidence of pulmonary seed embolism in patients treated with linked seeds.

It is conceivable that other dosimetric arrangements of linked seeds that place a higher percentage of the activity in the periphery of the gland could eliminate the need for free seeds centrally with a presumed further reduction in pulmonary seed emboli. Alternatively, free seed implant techniques could be employed that attempt to restrict seed placement to the prostate itself without implanting an extraprostatic margin. This would theoretically eliminate placement of seeds into the periprostatic venous plexus region, but would reduce the effective treatment margin. Whether these approaches would be successful in preventing seed emboli, and also achieve equivalent long-term outcomes comparable to our results has yet to be demonstrated.

CONCLUSION

1. Radioactive seed pulmonary embolism is a recognized consequence of free seed prostate brachytherapy. The incidence in our series was 11.6%.
2. There appears to be no acute effects associated with radioactive seed pulmonary embolism.
3. There are no significant detrimental dosimetric effects in the prostate from seed loss through pulmonary embolism using the "Seattle" brachytherapy technique.
4. Linked seeds in peripheral needles can dramatically reduce the incidence of radioactive seed pulmonary embolism (0.7%) compared to free seed implants (11.6%).

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